10/560,319 Page 4

L1 STRUCTURE UPLOADED

=> d l1

L1 HAS NO ANSWERS

L1 STR

G1 Cb, Ak

Structure attributes must be viewed using STN Express query preparation.

=> s l1 SAMPLE SEARCH INITIATED 10:47:16 FILE 'REGISTRY' SAMPLE SCREEN SEARCH COMPLETED - 78 TO ITERATE

100.0% PROCESSED 78 ITERATIONS 8 ANSWERS

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*

BATCH \*\*COMPLETE\*\*

PROJECTED ITERATIONS: 1031 TO 2089

PROJECTED ANSWERS: 8 TO 329

L2 8 SEA SSS SAM L1

=> s l1 sss full FULL SEARCH INITIATED 10:47:26 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 1309 TO ITERATE

100.0% PROCESSED 1309 ITERATIONS 75 ANSWERS

SEARCH TIME: 00.00.01

L3 75 SEA SSS FUL L1

=> file caplus

COST IN U.S. DOLLARS SINCE FILE TOTAL

ENTRY SESSION

FULL ESTIMATED COST 172.10 172.31

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FILE COVERS 1907 - 14 Dec 2007 VOL 147 ISS 26 FILE LAST UPDATED: 13 Dec 2007 (20071213/ED)

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http://www.cas.org/infopolicy.html

=> s 13

L4

11 L3

=> d ibib abs hitstr tot

L4 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2007 ACS ON STN ACCESSION NUMBER: 2007:1333355 CAPLUS

DOCUMENT NUMBER: 147:541903 TITLE:

147:541903 Preparation of azetidinyl compounds as neurokinin antagonists for treating gastrointestinal disorder Johansson, Anders INVENTOR(S):

PATENT ASSIGNEE(S): SOURCE: Swed. U.S. Pat. Appl. Publ., 13pp. CODEN: USXXCO

DOCUMENT TYPE: LANGUAGE: English 2

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE US 2007270400 PRIORITY APPLN. INFO.: A1 20071122 US 2007-749984 US 2006-801576P

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

The present invention relates to new compds. of formula I (wherein Het

for example, substituted piperazine), to pharmaceutical compns.

for example, substituted piperaxine; to pharmaceuter composition said compds., and to the use of said compds in therapy. I are neurokinin antagonists with well-balanced pharmacokinetic and pharmacokynamic properties useful for treating functional gastrointestinal disorder, IBS and functional dyspepsis. The present invention further relates to processes for the preparation of compds of formula 1. For example, II

processes for the preparation of compds. Of formula 1. For example, II prepared by reacting 3-Chloro-N-[(25)-2-(4-fluorophenyl)-4-oxobutyl]-N-methyl-5-(trifluoromethyl)benzamide and etyl-4-azetidin-3-ylpiperazine hydrochloride. In in vitro testing II had pKB values of 7.2-8 for human NK1, NK2, and NK3 receptors. 957127-68-1P, 3-Chloro-N-[(25)-2-(4-fluorophenyl)-4-(3-(4-acetylpiperazin-1-yl)lazetidin-1-yl]butyl]-N-methyl-5-(trifluoromethyl)benzamide 957127-70-7P, 3-Chloro-N-[(25)-2-(4-fluorophenyl)-4-[3-(4-isobutyrylpiperazin-1-yl)lazetidin-1-yl]butyl]-N-methyl-5-(trifluoromethyl)benzamide
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); TMU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses).

(Uaea),

(drug candidate; preparation of azetidinylpiperidine compds. as metabolically stable neurokinin antagonists for treating gastrointestinal disorders)
95/127-68-3 CAPLUS
Benzamide, N-{(2S)-4-[3-{4-acetyl-1-piperazinyl}-1-azetidinyl]-2-(4-

ANSWER 2 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER 2007:1333249 CAPLUS 147:541905 DOCUMENT NUMBER:

147:54:905
Preparation of morpholinylazetidines as neurokinin receptor antagonists for treating gastrointestinal disorders
Predenwall, Marlene; Johansson, Anders
Swed.
U.S. Pat. Appl. Publ., 10pp.
CODEN: USXXCO TITLE:

INVENTOR(S):

PATENT ASSIGNEE(S): SOURCE:

DOCUMENT TYPE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO 100711122 US 2007-749951 200705167 W0 2007-55484 20070516 AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, VC, VN, ZA, ZM, ZW
CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, CM, CM, TL, PL, PT, RO, SE, SI, SK, TR, BF, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BM, AZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, TJ, TM A1 2 A2 AM, AT, CR, CU, GM, GT, K2, LA, MY, MZ, SD, SE, US, UZ, CH, CY, LU, LV, CI, CM, LS, MW, MD, RU, US 2007270399 WO 2007136326 PRIORITY APPLN US 2006-801578P

Gİ

\* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT \*

The present invention relates to new compds. of formula I (wherein Rl is C1-C4 alkyl, optionally substituted by ≥ 1 fluoro atoms), to pharmaceutical compns. comprising said compds., and to the use of said compds in therapy. I are neurokinin antagonists with well-balanced pharmacokinetic and pharmacodynamic properties useful for treating gastrointestinal disorders including ISS and functional dyspepsia. The present invention further relates to processes for the preparation of ds.

compds.

of formula I. For example, II was prepared by reacting
3-chloro-N-[(2S)-2(4-fluorophenyl)-4-oxobutyl]-N-methyl-5-(trifluoromethyl)benzamide and
4-azetidin-2-yl/morpholine hydrochloride. In in vitro testing II had pKB
values of 6.9-7.6 for human NKI, NK2, and NK3 receptore.

IT 957111-63-6P, 3-Chloro-N-(12S)-2-(4-fluorophenyl)-4-[3-(morpholin4-yl)azetidin-1-yl]butyl]-N-methyl-5-(trifluoromethyl)benzamide
957111-72-7P, 3-Chloro-N-[-2-(4-fluorophenyl)-4-[3-(morpholin4-yl)azetidin-1-yl]butyl]-N-methyl-5-(trifluoromethyl)benzamide
957111-73-8P, [8]-3-Chloro-N-[-2-(4-fluorophenyl)-4-[3-(morpholin4-yl)azetidin-1-yl]butyl]-N-methyl-5-(trifluoromethyl)benzamide
957111-74-9P, 3-Chloro-N-[-2-(4-fluorophenyl)-4-[3-(morpholin4-yl)azetidin-1-yl]butyl]-N-methyl-5-(trifluoromethyl)benzamide
957111-74-9P, 3-Chloro-N-[-2-(4-fluorophenyl)-4-[3-(morpholin4-yl)azetidin-1-yl]butyl]-N-methyl-5-(trifluoromethyl)benzamide

ANSWER 1 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Confluorophenyl)butyl)-3-chloro-N-methyl-5-(trifluoromethyl)-NAME) (Continued)

Absolute stereochemistry

957127-70-7 CAPLUS Benzamide, 3-chloro-N-[(2S)-2-(4-fluorophenyl)-4-[3-[4-(2-methyl-1-

oxopropyl) -1-piperazinyl] -1-azetidinyl}butyl) -N-methyl-5-(trifluoromethyl) -(CA INDEX NAME)

Absolute stereochemistry

ANSWER 2 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued) yllazetidin-1-yllbutyll-N-methyl-5-(trifluoromethyl)benzamide RL: ADV (Adverse effect, including Coxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; prepn. of morpholinylazetidines as neurokinin

antagonists for treating gastrointestinal disorders)
957111-63-6 CAPLUS
Benzamide, 3-chloro-N-[(2S)-2-(4-fluorophenyl)-4-[3-(4-morpholinyl)-1azetidinyl]butyl]-N-methyl-5-(trifluoromethyl)- (CA INDEX NAME)

957111-72-7 CAPLUS Beardamid-3-(4-fluorophenyl)-4-(3-(4-morpholinyl)-1-aezeidinyl)buryl)-5-(trifluoromethyl)- (CA INDEX NAME)

957111-73-8 CAPLUS
Benzamide, 3-chloro-N-ethyl-N-{(2S)-2-(4-fluorophenyl)-4-{3-{4-morpholinyl}-1-azetidinyl}butyl}-5-(trifluoromethyl)- (CA INDEX NAME)

ANSWER 2 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

957111-74-9 CAPLUS
Benzamide, 3-chloro-N-{2-(4-fluorophenyl)-4-{3-(4-morpholinyl)-1-azetidinyl}butyl}-N-methyl-5-(trifluoromethyl)- (CA INDEX NAME)

ANSWER 3 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

fluoropheny1) -4- [3- [4-[(morpholin-4-yl)carbonyl]piperidin-1-yl]ezetidin-1-yl]butyl]-N-methyl-5-(trifluoromethyl)benzamide
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PAT (Pharmacokinetice): SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(drug candidate; prepn. of azetidinylpiperidine compds. as neurokinin antagonists for treating gastrointestinal disorders) 957054-68-1 CAPLUS INDEX NAME NOT YET ASSIGNED

Absolute stereochemistry

957054-70-5 CAPLUS
4-Piperidinecarboxamide, 1-{1-{(3S)-4-{{3-bromo-5-(trifluoromethyl)benzoyl]methylamino}-3-(4-fluorophenyl)butyl}-3-azetidinyl}-N,N-dimethyl- (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSMER 3 OF 11 CAPLUS COPYRIGHT 2007 ACS ON STN
ACCESSION NUMBER: 2007:1333221 CAPLUS
DOCUMENT NUMBER: 17:541739
TITLE: Preparation of azetidinyloiper

147:541739
Preparation of azetidinylpiperidine compounds as neurokinin antagonists for treating gastrointestinal

neurokinin antagonists for treating gastrointestind disorders
Johansson, Anders; Johansson, Johan; Sigfridsson, Carl-Gustav
Swed.
U.S. Pat. Appl. Publ., 16pp.
CODEN: USXXCO
Patent
English
2 INVENTOR(S):

PATENT ASSIGNEE(S): SOURCE:

DOCUMENT TYPE: LANGUAGE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. US 2007270398 PRIORITY APPLN. INFO.: US 2007-747322 US 2006-801577P 20071122

GI

STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT •

The present invention relates to new compds. of formula I (wherein R1 and R2 are independently H, Me, and Et, or R1 and R2 form a 4-6-membered ring together with the amide nitrogen, said ring optionally containing an

oxygen
atom; and X is Br or Cl), to pharmaceutical compns. comprising said
compds., and to the use of said compds. in therapy. I are neurokinin
antagonists with well-balanced pharmacokinetic and pharmacodynamic
properties useful for treating functional gastrointestinal disorder, IBS
and functional dyspepsia. The present invention further relates to
processes for the preparation of compds. of formula I. For example, II

prepared by reacting
ono.N-[(25)-2-(4-fluorophenyl)-4-oxobutyl]-N-methyl5-(trifluoromethyl)benzamide and 1-azetidin-3-yl-4-(azetidin-1ylcarbonyl)piperidine. In in vitro testing II had pKB values of 7-9 for
human NKI, NK2, and NK3 receptors.
957054-68-1P, N-[(25)-4-[3-4-(Azetidin-1-yl)carbonyl]piperidin-1yl]azetidin-1-yl]-2-(4-fluorophenyl)butyl]-3-bromo-N-methyl-5(trifluoromethyl)benzamide 957054-70-5P, 1-[1-[(3S)-4-[[3-Bromo-

5-(trifluoromethyl)benzoyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl]-N,N-dimethylpiperidine-4-carboxamide 957054-71-69,
1-(1-[(3S)-4-[[3-Bromo-5-(trifluoromethyl)benzoyl](methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3-yl]-N,N-dimethylpiperidine-4-carboxamide diformate 957054-73-8P, 1-[1-{(3S)-4-[[3-Bromo-5-

(trifluoromethyl)benzoyl] (methyl)amino]-3-(4-fluorophenyl)butyl]azetidin-3yl]piperidine-4-carboxamide 957054-76-1P, 3-Bromo-N-{(2S)-2-(4-

ANSWER 3 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

957054-71-6 CAPLUS
Formic acid, compd. with 1-[1-{(15)-4-[[3-bromo-5-(trifluoromethyl]benzoyl]methylamino]-3-(4-fluorophenyl)butyl]-3-azetidinyl]-N,N-dimethyl-4-piperidinecarboxamide (2:1) (CA INDEX NAME)

CRN 957054-70-5 CMF C30 H37 Br F4 N4 O2

ANSWER 3 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

(Continued)

O== CH- OH

957054-73-8 CAPLUS
4-Piperidinecarboxamide, 1-{1-{(3S)-4-{{3-bromo-5-(rrifluoromethyl) benzoyl}methylamino}-3-(4-fluorophenyl)butyl}-3-azetidinyl}- (CA INDEX NAME)

Absolute stereochemistry.

957054-76-1 CAPLUS
Benzamide, 3-bromo-N-[(2S)-2-(4-fluorophenyl)-4-[3-[4-(4-morpholinyl)-1-piperidinyl)-1-azetidinyl)butyl]-N-methyl-5-(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry

ANSWER 3 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

CM 2

110-16-7 C4 H4 O4

Double bond geometry as shown

ANSWER 3 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

957054-75-0P RL: PAC (Pharmacological activity); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (drug candidate; preparation of azetidinylpiperidine compds. as

CRN 957054-73-8 CMF C28 H33 Br F4 N4 O2

```
L4 ANSMER 4 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:438599 CAPLUS DOCUMENT NUMBER: 146:408217
TITLE: Novel crystalline form of 3,5-dibromo-n-((2s)-2-(-4-
 fluorophenyl)-4-(3-morpholin-4-ylaztidin-1-yl)butyl]-n
methylbenzamide, modification B
Ahlqvist, Matti
Ablqvist, Matti
AssIGNEE(S):
SOURCE:
PITT 1, Appl., 17pp.
COODEN: PIXXD2
DOCUMENT TYPE:
LANGUAGE:
PAMILY ACC. NUM. COUNT:
PAMENT MERCHANICALS
PAMILY ACC. NUM. COUNT:
1
  DOCUMENT TYPE:
LANGUAGE:
FAMILY ACC. NUM. COUNT:
PATENT INFORMATION:
                                                                            DATE
              PATENT NO.
KIND
                                                                                                         APPLICATION NO.
                                                                                                                                                               DATE
            The present invention relates to a novel crystalline form of 3.5-dibromo·N-[(2S)-2-(4-fluorophenyl)-4-(3-morpholin-4-ylazetidin-1-yllbutyl]-N-methylbenzamide(I). Further, the present invention also relates to the use of the novel crystalline form for the treatment of gastrointestinal disorders, pharmaceutical compns. containing it as well
              processes for the preparation of the novel crystalline form. I was
 processes for the prepassion. It is always to be sold material was then isolated by acctonitrile and the resulting solid material was then isolated by filtration and washed with acctonitrile. The solid was shown by X-ray powder diffraction to be a mixture of two or more crystal modifications. Modification B of I was crystallized by slurring the solid from the
 previous atep in Et acetate in room temperature overnight. The solid material was then
              isolated by evaporation of the solvent under a purge of nitrogen which
            showed to be pure modification B I. Modification B melted with a m.p. onset of 117° and may be identified by the X-ray powder diffraction. 810679-97-1 RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study);
             (novel crystalline form of morpholin methylbenzamide derivative) 810679-97-1 CAPLUS Benzamide, 3,5-dibromo-N-[(2S)-2-(4-fluorophenyl)-4-[3-(4-morpholinyl)-1-
```

ANSWER 4 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN azetidinyl]butyl]-N-methyl- (CA INDEX NAME)

(Continued)

Absolute stereochemistry.

REFERENCE COUNT:

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

ANSWER 5 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

REFERENCE COUNT

THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

L4 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:433836 CAPLUS
DOCUMENT NUMBER: 146:408215
TITLE: Novel crystalline form of 3,5-dibromo-n-[(28)-2-(-4fluorophenyl)-4-(3-morpholin-4-ylazetidin-1-yl)butyl]
INVENTOR(S):

PATENT ASSIGNEE(S):

SOURCE:

DOCUMENT TYPE:

LANGUAGE:

PAMILY ACC. NUM. COUNT:

PATENT TAPPMATION:

PATENT TAPPMAT DOCUMENT TYPE: LANGUAGE: PAMILY ACC. NUM. COUNT: PATENT INFORMATION: DATE

20070419 MO 2006-SS1128 20061004
AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, VN, ZA, ZM, ZW
CZ, DE, DK, EE, ES, FI, PR, GB, GR, HU, IE, MG, MI, MP, NE, SF, SK, TR, BF, BJ, GN, GO, GW, ML, MR, NE, SN, TD, TO, BW, GH, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, TM PATENT NO. DATE APPLICATION NO. DATE WNO 2007043939 A1 2

W: AE, AG, AL, AM, AT,
CN, CO, CR, CU, CZ,
GE, GH, GM, HN, HR,
KR, KZ, LA, LC, LK,
MM, MX, MY, MZ, AM,
RU, SC, SD, SE, SG,
UA, UG, US, UZ, VC,
RN: AT, BE, BG, CH, CY,
IS, IT, LT, LU, LV,
CP, CG, CI, CM, GA,
GM, KE, LS, MM, MZ,
KG, KZ, MD, RU, TJ,
PRIORITY APPLN. INFO:: SE 2005-2221 A 20051007 The present invention relates to a novel crystalline form of 3,5-dibromo-N-[(2S)-2-(4-fluorophenyl)-4-(3-morpholin-4-ylazetidin-1-yl)butyl]-N-methylbenzamide(1). Further, the present invention also relates to the use of the novel crystalline form for the treatment of gastrointestinal disorders, pharmaceutical compns. containing it as well processes for the preparation of the novel crystalline form. I was slurried in 5  $\ensuremath{\text{mL}}$ ried in 5 mL actionistic and the resulting solid material was then isolated by filtration, washed with acetonistrile, and dried. The solid was shown to be pure modification A of I. Modification A melted with a m.p. onset of 188° and may be identified by the X-ray powder diffraction. ΙT RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (novel crystalline form of morpholin methylbenzamide derivative)

RIGORY CTYPE AND THE STATE STA Absolute stereochemistry.

L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS ON STN

ACCESSION NUMBER: 2007:382485 CAPLUS

DOCUMENT NUMBER: 146:379804

Azetidine compounds as neurokinin receptor antagonists, their preparation, pharmaceutical compositions, and use in therapy

Bergman, Rolf; Holmqvist, Sara: Von Unge, Sverker Astracenca As, Swed.

PATENT ASSIGNEE(S): Astracenca As, Swed.

DOCUMENT TYPE: PATENT ACC. NUM. COUNT: 1 DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: PATENT NO.

KIND DATE XIND DATE APPLICATION NO. DATE

A1 20070405 MC 2006-SE1092 20060927
AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, NR,
MZ, NA, NG, NI, NO, NZ, OM, PO, PH, PL, PT, RO, RS,
SS, SG, SS, SL, SM, SW, SY, TJ, TM, TN, TR, TT, TZ,
UZ, VC, VN, ZA, ZM, ZW
CH, CY, CZ, DE, DX, EE, ES, PI, FR, GB, GR, HU, IE,
LU, LV, MC, NI, PL, PT, RO, SE, SI, SK, TR, BF, BJ,
CM, GA, GN, GO, GW, ML, MR, NE, SN, TD, TG, BM, GH,
MM, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZN, AM, AZ, BR,
RU, TJ, TM

SE 2005-2150 A 20056027 APPLICATION NO. DATE WO 2007037743 W: AE, AG AE, AG, AL, CN, CO, CR, GE, GH, GM, KR, KZ, LM, MY, RU, SC, SD, AT, BE, BG, IS, IT, LT, CF, CG, CI, GM, KE, LS, KG, KZ, KD, LN, INFO: PRIORITY APPLN. INFO.: SE 2005-2150 A 20050929 OTHER SOURCE(S): MARPAT 146:379804

. STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT .

The invention relates to azetidine compds. of formula I, which are neurokinin (NK) receptor antagonists. In compds. I, Het is II or III. where Ar is 4-FC6H4; R is Cl-4 alkyl, cyclopropyl, Cl-4 methoxyalkyl,

ethoxyalkyl, Cl-4 hydroxyalkyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydropyran-2-yl, tetrahydropyran-4-yl; and Yis Cl-3 alkylene, 'GH2OG12-, or 'GH2CH3O-; including salts end enantiomers thereof. The invention also relates to the the preparation

of I , pharmaceutical compns. comprising a compound I as active ingredient and a pharmaceutically acceptable carrier or diluent, as well as to the use of the compns. for the treatment of functional gastrointestinal disorders, irritable bowel syndrome (IBS), and functional dyspepsia. Substitution

of

1-(diphenylmethyl)-azetidin-3-yl methanesulfonate with pyrrolopyrazinone
IV followed by deprotection gave azetidine V. Amidation of
3-bromo-5-trifluoromethylbenzoic acid with
(S)-N-[2-(4-fluorophenyl)-pent4-en-1-yl]methylemine resulted in the formation of benzamide VI, which
underwent oxidation with osmium tetroxide and sodium periodate followed

ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued) reductive amination with azetidine V to give the dihydrochloride of VII. The compds. of the invention are antagonists of NK receptors, e.g.,

The compds. of the invention are antagonists of NK receptors, e.g., d.

VII expressed pKB values of 8.7, 7.8, and 8.5 for NK1, NK2, and NK3 receptors, reap.

930783-06-5P 930783-07-6P, 3-Bromo-N-{(2S)-2-(4-fluoropheny)1-4-[3-(4-fluoropheny)1-4-[3-(4-fropionylpiperazin-1-y1)azetidin-1-y1]buty1]-N-methy1-5-(trifluoromethy1)benzamide dihydrochloride 930783-09-8P 930783-10-1P, 3-Bromo-N-{(2S)-2-(4-fluoropheny)1-4-(3-(4-fluoromethy1)benzamid-930783-11-y1)buty1]-N-methy1-5
(trifluoromethy1)benzamide 930783-11-2P 930783-14-5P 930783-15-6P, 3-Bromo-N-{(2S)-4-(3-(4-butyrylpiperazin-1-y1)azetidin-1-y1]benzamide dihydrochloride 930783-16-7P, 3-Bromo-N-{(2S)-2-(4-fluoropheny1)-4-(3-(4-ie)butyrylpiperazin-1-y1)azetidin-1-y1]buty1]-N-methy1-5-(trifluoromethy1)benzamide dihydrochloride 930783-20-3P 930783-21-4P,

3-Bromo-N-(2s)-4-(3-(4-(cyclopropylcarbonyl)piperazin-1-yl)azetidin-1-yl)2-(4-fluorophenyl)butyl)-N-methyl-5-(trifluoromethyl)benzamide
930783-22-5P, 3-Bromo-N-((2s)-4-(3-(4-butyrylpiperazin-1yl)azetidin-1-yl)-2-(4-fluorophenyl)butyl)-N-methyl-5(trifluoromethyl)benzamide 930783-23-6P, 3-Bromo-N-((2s)-2-(4fluorophenyl)-4-(13-(4-laobutyrylpiperazin-1-yl)azetidin-1-yl)butyl)-Nmethyl-5-(trifluoromethyl)benzamide
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
(Therapeutic use); BIOL (Biological actudy); PREP (Preparation); USES
(Uses)
(drug candidate; preparation of azetidine deriva. as neurokinin
receptor

(drug candidate; preparation of usual and a secondary antagoniata)

RN 930783-06-5 CAPAUS

CN Benzamide, N-[(28)-4-[3-(4-acetyl-1-piperazinyl)-1-azetidinyl)-2-(4-fluorophenyl)butyl)-3-bromo-N-methyl-5-(trifluoromethyl). (CA INDEX

Absolute stereochemistry

ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

930783-10-1 CAPLUS
Benzamide,
Grow-N-[(25)-2-(4-fluorophenyl)-4-(3-[4-(2-methoxyacetyl)-1piperazinyl]-1-azetidinyl]butyl]-N-methyl-5-(trifluoromethyl)- (CA INDEX
NAME)

Absolute stereochemistry.

930763-11-2 CAPLUS
Benzamide,
Goo.N-[(125)-2-(4-fluorophenyl)-4-[3-[4-(2-hydroxyacetyl)-1piperazinyl]-1-azetidinyl]butyl]-N-methyl-5-(trifluoromethyl)- (CA INDEX
NAME)

Absolute stereochemistry.

L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

930783-07-6 CAPLUS
Benzamide, 3-bromo-N-{(2S)-2-(4-fluorophenyl)-4-[3-(4-(1-oxopropyl)-1-piperazinyl]-1-azetidinyl]butyl]-N-methyl-5-(trifluoromethyl)-, hydrochloride (1:2) (CA INDEX NAME)

PAGE 2-A

●2 HC1

930783-09-8 CAPLUS Benzamide, 3-bromo·N-[(2S)-2-(4-fluorophenyl)-4-[3-[4-[(tetrahydro-2-furanyl)carbonyl]-1-piperazinyl]-1-azetidinyl]butyl]-N-methyl-5-(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

930783-14-5 CAPLUS

Absolute stereochemistry.

PAGE 2-A

●2 HC1

930783-15-6 CAPLUS

Benzamide, 3-hormo-N-[(28)-2-(4-fluorophenyl)-4-(3-[4-(1-oxobutyl)-1-piperazinyl]-1-azetidinyl]butyl]-N-methyl-5-(trifluoromethyl)-.

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ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN hydrochloride (1:2) (CA INDEX NAME) (Continued)

Absolute stereochemistry.

PAGE 2-A

930783-16-7 CAPLUS Benzamide, 3-bromo-N-[(2S)-2-(4-fluorophenyl)-4-[3-[4-(2-methyl-1-

oxopropy1)-1-piperaziny1]-1-azetidiny1]buty1]-N-methy1-5-(trifluoromethy1), hydrochloride (1:2) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN PAGE 1-A

PAGE 2-A

(Continued)

930783-20-3 CAPLUS
Benzamide, 3-bromo-N-[(2S)-2-(4-fluorophenyl)-4-(3-[4-(1-oxopropyl)-1-piperazinyl]-1-azetidinyl]butyl]-N-methyl-5-(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

Absolute stereochemistry.

930783-22-5 CAPLUS
Benzamide, 3-bromo-N-{(2\$)-2-(4-fluorophenyl)-4-[3-[4-(1-oxobutyl)-1-piperazinyl]-1-azetidinyl]butyl}-N-methyl-5-(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

930783-23-6 CAPLUS Benzamide, 3-bromo-N-[(2S)-2-(4-fluorophenyl)-4-[3-[4-(2-methyl-1-

oxopropyl)-1-piperazinyl)-1-azetidinyl]butyl]-N-methyl-5-(trifluoromethyl)-

L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RN 930783-21-4 CAPLUS
COPYRIGHT 2007 ACS on STN (Continued)
S-bromo-N-[(2S)-4-{3-{4-(cyclopropylcarbonyl)-1-piperazinyl}-1-azetidinyl]-2-(4-fluorophenyl)butyl]-N-methyl-5-(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry

ANSWER 6 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (CA INDEX NAME)

THERE ARE 11 CITED REFERENCES AVAILABLE FOR

FORMAT

RECORD. ALL CITATIONS AVAILABLE IN THE RE

L4 ANSWER 7 OP 11 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1356802 CAPLUS
146:100541 Preparation of azetidine derivatives as neurokinin receptor antagonists for treatment of

gastrointestinal diseases

diseases
Holmqvist, Sara; Johansson, Anders; Svensson, Arne;
Von Unge, Sverker
Astrazeneca AB, Swed.
PCT int. Appl., SJpp.
CODEN: PIXXD2
Patent
English
1 INVENTOR (S):

PATENT ASSIGNEE(S): SOURCE:

DOCUMENT TYPE:

LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

|    | PAT     | PATENT NO.    |     |      |     |            | KIND |               | DATE |     | APPLICATION NO. |      |      |     |          | DATE |      |     |  |
|----|---------|---------------|-----|------|-----|------------|------|---------------|------|-----|-----------------|------|------|-----|----------|------|------|-----|--|
|    |         |               |     |      | -   |            |      | WQ 2006-SE759 |      |     |                 |      |      |     |          |      |      |     |  |
|    | WO      | WO 2006137790 |     |      |     | A1 2006122 |      |               |      |     |                 |      | 1226 |     | 20060621 |      |      |     |  |
|    |         | W:            | AE, | AG,  | AL, | AM,        | AT,  | AU,           | AZ,  | BA, | BB,             | BG,  | BR,  | BW, | BY,      | BZ,  | CA,  | CH, |  |
|    |         |               | CN, | co,  | CR, | CU,        | CZ,  | DE,           | DK,  | DM, | DZ,             | EC,  | EE,  | EG, | ES,      | FI,  | GB,  | GD, |  |
|    |         |               | GE, | GH,  | GM, | HN,        | HR,  | HU,           | ID.  | IL, | IN,             | IS,  | JP,  | KE, | KG,      | KM,  | KN.  | KP. |  |
|    |         |               | KR, | KZ,  | LA. | LC.        | LK,  | LR,           | LS,  | LT, | LU,             | LV,  | LY,  | MA, | MD,      | MG.  | MK.  | MN. |  |
|    |         |               | MW, | MX,  | MZ, | NA,        | NG,  | NI,           | NO,  | NZ, | OM,             | PG,  | PH,  | PL, | PT,      | RO,  | RS,  | RU, |  |
|    |         |               | SC. | SD,  | SE, | SG,        | SK,  | SL,           | SM,  | SY, | TJ,             | TM,  | TN,  | TR, | TT,      | TZ.  | UA,  | UG, |  |
|    |         |               | US, | UŽ,  | VC, | VN,        | ZA,  | ZM,           | ZW   |     |                 |      |      |     |          |      |      |     |  |
|    |         | RW:           | AT, | BE,  | BG, | CH,        | CY.  | CZ,           | DE,  | DK, | EE.             | ES,  | FI,  | FR, | GB,      | GR,  | HU.  | IE, |  |
|    |         |               |     |      |     |            |      | MC.           |      |     |                 |      |      |     |          |      |      |     |  |
|    |         |               | CF. | CG.  | CI. | CM.        | GA.  | GN.           | GO.  | GW, | ML.             | MR.  | NE,  | SN. | TD.      | TG.  | BW.  | GH. |  |
|    |         |               | GM. | KE.  | LS. | MW.        | MZ.  | NA.           | SD.  | SL. | SZ.             | TZ.  | UG.  | ZM. | ZW.      | AM.  | AZ.  | BY. |  |
|    |         |               | KG. | KZ.  | MD. | RU.        | TJ.  | TM            |      |     |                 |      |      |     |          |      |      |     |  |
| PI | RIORITY | APP           | LN. | INFO | . : |            |      |               |      |     | SE 2            | 005- | 1494 |     |          | A 2  | 0050 | 623 |  |

OTHER SOURCE(S):

MARPAT 146:100541

(Continued)

ANSWER 7 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

RN 917572-11-3 CAPLUS
CN Benzamide,
3,5-dibromo-N-[(2S)-2-(4-fluorophenyl)-4-[3-[2-(hydroxymethyl)1-piperazinyl)-1-azetidinyl)butyl}-N-methyl-, hydrochloride (1:3) (CA
INDEX NAME)

Absolute stereochemistry.

●3 HC1

917572-12-4 CAPLUS Benzamide, 3-bromo-N- $\{(2S)-2-(4-fluorophenyl)-4-\{3-\{(3R)-3-(2-hydroxyethyl)-4-morpholinyl]-1-ezetidinyl<math>\}$ butyl $\}$ -N-methyl-5- $\{(xrifluoromethyl)-(CA INDEX NAME)\}$ 

ANSWER 7 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

The title compds. with general formula I (wherein R2 = (un)substituted C1-4 alkyl; R3 = (CH2) $\operatorname{nc}(R6)$  (R7)OH, where n = 0-3; R6 and R7 = independently H or methyl; X = 0 or (un)substituted NH; Ar = substituted Ph, naphthyl, etc.] or pharmaceutically acceptable salts thereof are prepared as neurokinin receptor antagonists for the treatment of gastrointestinal diseases. For example, the compound II was prepared in

multi-step synthesis. II showed antagonistic activity with PKB value of 8.1, 7.6, and 7.1 against NKI, NK2, and NK3 receptors, resp. II also showed statistically significant CYP3A4 inhibitory activity with ICSO value of 19.2 µM.
917572-08-8P 917572-11-3P 917572-12-4P
917572-14-6P 917572-15-7P
RL: PAC (Pharmacological activity); SFN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation): USES (Uses)

(Uses) (preparation of azetidine derivs, as neurokinin receptor antagonists

torestment of gastrointestinal diseases)

RN 917572-08-8 CAPLUS

Benzamide,

3,5-dibromo-N-{(2S)-2-(4-fluorophenyl)-4-(3-(2-hydroxyethyl)-1-pieraxinyl)-1-azetidinyl]butyl]-N-methyl-, hydrochloride (1:3) (CA INDEX NAME)

L4 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN Absolute stereochemistry.

917572-14-6 CAPLUS
Benzamide, 3,5-dibromo-N-{{2S}-2-{4-fluorophenyl}-4-{3-{(3R)-3-{2-hydroxyethyl}-4-morpholinyl}-1-azetidinyl}butyl}-N-methyl- (CA INDEX NAME)

Absolute stereochemistry

917572-15-7 CAPLUS
Benzamide, 3,5-dibromo-N-{{2S}-2-(4-fluorophenyl)-4-{3-{(3R)-3-(hydroxymethyl)-4-morpholinyl]-1-azetidinyl}butyl}-N-methyl- (CA INDEX NAME)

ANSWER 7 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

917572-17-9P 917572-24-8P RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation of ezetidine derivs. as neurokinin receptor antagonists

treatment of gastrointestinal diseases)
917572-17-9 CAPLUS
1-Piperazinecarboxylic acid, 4-[1-[(35)-4-[(3,5-dibromobenzoyl)methylamino]-3-(4-fluorophenyl)butyl]-3-azetidinyl]-3-(2-hydroxyethyl)-, 1,1-dimethylethyl ester (CA INDEX NAME)

Absolute stereochemistry.

917572-24-8 CAPLUS

911572-24-8 CAPLUS
1-Piperazinecarboxylic acid, 4-[1-[(3S)-4-[(3,5-dibromobenzoyl)methylamino]-3-(4-fluorophenyl)butyl)-3-azetidinyl]-3-

L4 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2006:1356559 CAPLUS DOCUMENT NUMBER: 146:100540

DOCUMENT NUMBER: TITLE:

Preparation of azetidine derivatives as neurokinin receptor antagonists for treatment of

gastrointestinal diseases Johansson, Anders; Johansson, Johan; Von Unge,

INVENTOR (S): Sverker PATENT ASSIGNEE(S):

SOURCE :

Astrazeneca AB, Swed. PCT Int. Appl., 76pp. CODEN: PIXXD2 Patent English 1 DOCUMENT TYPE:

FAMILY ACC. NUM. COUNT: PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO MO 2006137791

W: AE, AG, AI

CN, CO, Cr

GE, GH, GR

K2, LC, LI

M2, NA, NC

SE, SG, SI

VC, VN, 22

RM: AT, BE, BC

1S, 1T, LI

CF, CG, CI

GM, KE, LE

RG, K2, MP

PRIORITY APPLN. INFO: WO 2006-SE760
BA, BB, BG, BR, BM,
DM, DZ, EC, EE, EG,
IN. IS, JP, KE, KG,
LV, LY, MA, MD, MG,
PG, PH, PL, PT, RO,
TM, TN, TR, TT, TZ, 20061228 , AU, AZ, , DE, DK, , ID, IL, , LT, LU, , NZ, OM, , SY, TJ, A1 AM, CU, HR, LR, NI, SL, ZM, CH, LU, CM, MW, RU, CZ, DE, DK, EE, ES, PI, PR, MC, NL, PL, PT, RO, SE, SI, GN, GQ, GW, ML, MR, NE, SN, NA, SD, SL, SZ, TZ, UG, ZM, TM

ANSWER 7 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Con (hydroxymethyl) -, 1,1-dimethylethyl ester (CA INDEX NAME) (Continued)

Absolute stereochemistry.

REFERENCE COUNT

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

The title compds. with general formula I [wherein R2 = (un)substituted Ci-4 alkyl; Het = 2,5-diazabicyclo[2.2.1]heptane, octahydropyrrolo[3,4-clpyrrole, 1,4-diazepane, etc.; Ar = substituted Ph, naphthyl, etc.] or pharmaceutically acceptable salts thereof are prepared as neurokinin receptor antagonists for the treatment of gestrointestinal diseases. For example, the compound II was prepared in a multi-step synthesis. I

11

ed antagonistic activity with pXB value of 7-9 against both NK1 and NK2 receptors, and pKB value of 6-9 against NK3 receptor. I also showed statistically significant CYPJA4 and hERG inhibitory activities with IC50 values of >2 µM and >10 µM, resp. 917609-69-99 RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RCT (Reactant); USES (Usea) (preparation of azetidine derivs. as neurokinin receptor antagonists

tor

treatment of gastrointestinal diseases)
917609-69-9 CAPLUS
Benzamide, N-{(2S)-4-{3-(4-amino-1-piperidinyl)-1-azetidinyl)-2-(4-fluorophenyl)butyl)-3,5-dibromo-N-methyl-, hydrochloride (1:3) (CA INDEX NAME)

L4 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

917609-70-2P 917609-72-4P 917609-73-5P 917609-79-1P 917609-83-7P RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) IT

(preparation of azetidine derivs. as neurokinin receptor antagonists for

for treatment of gastrointestinal diseases)

RN 917609-70-2 CAPLUS

CN Benzamide,
N-[(2S)-4-{3-[4-(aminomethyl)-1-piperidinyl}-1-azetidinyl]-2-{4fluorophenyl)butyl]-3,5-dibromo-N-methyl- (CA INDEX NAME)

ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN lute stereochemistry. (Continued)

917609-83-7 CAPLUS
Benzamide, 3,5-dibromo-N-{(2S)-4-{3-{4-(dimethylamino)-1-piperidinyl}-1-azetidinyl}-2-(4-fluorophenyl)butyl}-N-methyl- (CA INDEX NAME)

917609-96-2P 917609-97-3P 917610-01-6P 917610-14-1P 917610-33-4P RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent) (preparation of azetidine derivs. as neurokinin receptor antagonists

treatment of gastrointestinal diseases)
917609-96-2 CAPLUS
Carbamic acid, N-{1-{1-{(35)-4-{(3,5-dibromobenzoyl)methylamino}-3-{4-fluorophenyl)butyl}-3-azetidinyl}-4-piperidinyl]-, 1,1-dimethylethyl

(CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

917609-72-4 CAPLUS

Benzamide, 3,5-dibromo-N-{{2S}-2-(4-fluorophenyl)-4-{3-(hexahydro-1H-1,4-diazepin-1-yl)-1-azetidinyl]butyl}-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

917609-73-5 CAPLUS Benzamide, dibromo-N-{(25)-2-(4-fluorophenyl)-4-{3-(4-(methylamino)-1-piperidinyl)-1-azetidinyl)butyl}-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

917609-79-1 CAPLUS
Benzamide, N-{(2S)-4-{3-{(3R)-3-(2-aminoethyl)-4-morpholinyl}-1-azetidinyl}-2-(4-fluorophenyl)butyl}-3,5-dibromo-N-methyl- (CA INDEX

ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

917609-97-3 CAPLUS Carbamic acid, N-[[1-[(3S)-4-[(3,5-dibromobenzoyl)methylamino]-3-(4-fluorophenyl)butyl]-3-azetidinyl]-4-piperidinyl]methyl]-1,1-dimethylethyl ester (CA INDEX NAME)

Absolute stereochemistry.

917610-01-6 CAPLUS
Carbamic acid, N-[1-[1-[(3S)-4-[(3.5-dibromobenzoyl)methylamino]-3-(4-fluorophenyl)butyl]-3-azetidinyl]-4-piperidinyl]-N-methyl-,
1,1-dimethylethyl ester (CA INDEX NAME)

ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

RN 917610-14-1 CAPLUS
CN Carbamic acid,
N-[2-[(3R)-4-[(1-(3S)-4-[(3,5-dibromobenzoyl)methylamino]-3{4-fluorophenyl)butyl]-3-azetidinyl}-3-morpholinyl]ethyl}-,
1,1-dimethylethyl ester (CA INDEX NAME)

917610-33-4 CAPLUS
1H-1,4-Diazepine-1-carboxylic acid, 4-[1-{(35)-4-{(3,5-dibromobenzyl)methylamino}-3-(4-fluorophenyl)butyl)-3-azetidinyl}hexahydro-, 1,1-dimethylethyl ester (CA INDEX NAME)

Absolute stereochemistry.

```
ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER:
                                    2006:558670 CAPLUS
145:40270
DOCUMENT NUMBER:
TITLE:
                                    Dual NK1/NK2 receptor antagonists for the treatment
                                   gastrointestinal disorders
Astin Nielsen, Maria
Astrazeneca AB, Swed.
PCT Int. Appl., 52 pp.
CODEN: PIXXD2
Patent
INVENTOR (5):
PATENT ASSIGNEE(S):
SOURCE:
DOCUMENT TYPE:
LANGUAGE:
                                   English
FAMILY ACC. NUM. COUNT:
PATENT INFORMATION:
       PATENT NO.
       WO 2006062478
W: AE, A
```

KIND DATE APPLICATION NO. E

6062478 A1 20660615 WO 2005-SE1866 2

AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BN, BY, BZ, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GS, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, Z, NA, MO, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, VN, YU, ZA, ZH, ZM

AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, ES, IT, TL, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, CF, CG, CI, CM, GA, GN, GO, GM, ML, MR, NE, SN, TD, TG, GN, KE, LS, MM, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, KG, KZ, ND, RU, TJ, TM 20051207
BY, BZ, CA, CH,
ES, FI, GB, GD,
KM, KN, KP, KR,
MK, MN, MW, MX,
RU, SC, SD, SE,
UG, US, UZ, VC,

PRIORITY APPLN. INFO:: SE 2004-3005 A 20041209

OTHER SOURCE(S): MARPAT 145:40270

AB The invention discloses the use of dual NKI/NK2 receptor antagonists for the treatment of functional gastrointestinal disorders, e.g. functional dyspepsia.

1 810678-98-9 810678-98-9D, enantiomers and salts 810679-02-8 810679-02-8D, enantiomers and salts 810679-04-0 810679-04-0 810679-04-0 810679-04-0 810679-04-0 810679-04-0 810679-04-0 810679-04-0 810679-14-1 810679-11-1D, enantiomers and salts 810679-16-4 810679-11-1D, enantiomers and salts 810679-21-1 810679-21-1 B10679-21-1 B10679-21-1 B10679-21-0 enantiomers and salts 810679-32-4 B10679-32-4 D, enantiomers and salts 810679-32-4 B10679-31-2 enantiomers and salts 810679-31-8 B10679-31-9 enantiomers and salts 810679-32-8 B10679-31-9 enantiomers and salts 810679-6-0 B10679-6-0 enantiomers and salts 810679-12-0 B10679-6-0 enantiomers and salts 810679-12-0 B10679-6-0 enantiomers and salts 810679-7-1 B10679-7-1 B10679-7-1 enantiomers and salts 810679-7-1 enantiomers 810679-1 enantiomers 810679-1 enantiomers 810679-1 enantiomers 8

ANSWER 8 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued) thiomorpholinyl)-1-azetidinyl}butyl}-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

810678-98-9 CAPLUS

Benzamide, 3,5-dichloro-N-{(2S)-2-(3,4-dichlorophenyl)-4-{3-(4-thiomorpholinyl)-1-azetidinyl]butyl}-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

810679-02-8 CAPLUS
Benzamide, N-[(2S)-2-{3,4-dichlorophenyl}-4-{3-(4-thiomorpholinyl}-1-azetidinyl]butyl}-3,5-difluoro-N-methyl- (CA INDEX NAME)

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued) .

810679-02-8 CAPLUS
Benzamide, N-{(2S}-2-(3,4-dichlorophenyl)-4-(3-(4-thiomorpholinyl)-1-azetidinyl]butyl]-3,5-difluoro-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

810679-04-0 CAPLUS
Benzamide, N-[{2S}-2-(3,4-dichlorophenyl)-4-{3-(4-thiomorpholinyl)-1-azetidinyl}butyl}-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

RN 810679-08-4 CAPLUS
CN Benzamide,
3-cyano-N-(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-thiomorpholinyl)-1-azetidinyl]butyl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

810679-16-4 CAPLUS
Benzamide, N-[2-(4-fluorophenyl)-4-[3-(4-thiomorpholinyl)-1azetidinyl]butyl]-N-methyl-3,5-bie(trifluoromethyl)- (CA INDEX NAME)

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-04-0 CAPLUS
Benzamide, N-{{25}-2-{3,4-dichlorophenyl}-4-{3-{4-thiomorpholinyl}-1-azetidinyl}butyl}-N-methyl-3,5-bis{trifluoromethyl}- (CA INDEX NAME)

RN 810679-08-4 CAPLUS
CN Benzamide,
3-cyano-N-[(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-thiomorpholinyl)-1-azetidinyl]butyl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

810679-16-4 CAPLUS
Benzamide, N-[2-(4-fluorophenyl)-4-[3-(4-thiomorpholinyl)-1-azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

810679-21-1 CAPLUS
Benzamide, 3-fluoro-N-[(2S)-2-(4-fluorophenyl)-4-(3-(4-morpholinyl)-1-azetidinyl}butyl}-N-methyl-5-(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

RN 810679-21-1 CAPLUS

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12/14/2007

ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
Benzamide, 3-fluoro-N-[(2S)-2-(4-fluorophenyl)-4-[3-(4-morpholinyl)-1azetidinyl}butyl]-N-methyl-5-(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

RN 810679-25-5 CAPLUS
CN Benzamide,
N-{(2S)-2-(3,4-dichlorophenyl)-4-[3-{4-fluoro-1-piperidinyl}-1azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

810679-25-5 CAPLUS

N-[(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-fluoro-1-piperidinyl)-1-azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-30-2 CAPLUS
Benzamide, N-[(2S)-2-(4-fluorophenyl)-4-[3-(4-fluoro-1-piperidinyl)-1-azetidinyl)butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

810679-30-2 CAPLUS
Benzamide, N-[(2S)-2-(4-fluorophenyl)-4-[3-(4-fluoro-1-piperidinyl)-1-azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

RN 810679-26-6 CAPLUS
CN Benzamide,
N-{(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-hydroxy-1-piperidinyl)-1azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

RN 810679-36-6 CAPLUS
CN Benzamide,
N-[(2S)-2-(3,4-dichlorophenyl)-4-(3-{4-hydroxy-1-piperidinyl}-1azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-32-4 CAPLUS
Benzamide, N-([25]-2-(4-fluoropheny1)-4-[3-(4-hydroxy-1-piperidiny1)-1aretidiny1]buty11-N-methy1-3,5-bis(trifluoromethy1)- (CA INDEX NAME)

Absolute stereochemistry.

810679-32-4 CAPLUS
Benzamide, N-(182)-2-(4-fluorophenyl)-4-[3-(4-hydroxy-1-piperidinyl)-1aretidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

(Continued)

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

RN 810679-33-5 CAPLUS
CN Benzamide,
3,5-dichloro-N-[(2S)-2-(4-fluorophenyl)-4-[3-(4-morpholinyl)-1-azetidinyl]butyl]-N-methyl- (CA INDEX NAME)

RN 810679-33-5 CAPLUS
CN Benzamide,
3,5-dichloro-N-[(2S)-2-(4-fluorophenyl]-4-(3-(4-morpholinyl)-1azetidinyl]butyl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-62-0 CAPLUS
Benzamide, 3,5-dichloro-N-[(2S)-2-(3,4-dichlorophenyl)-4-(3-(1-oxido-4-thiomorpholinyl)-1-ezetidinyl]butyl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

810679-62-0 CAPLUS
Benzamide, 3,5-dichloro-N-{{2S}-2-{3,4-dichlorophenyl}-4-{3-(1-oxido-4-thiomorpholinyl}-1-ezetidinyl}butyl}-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-54-0 CAPLUS
Benzamide, 3,5-dibromo-N-[(2S)-2-(4-fluorophenyl)-4-[3-(4-hydroxy-1-piperidinyl)-1-azetidinyl]butyl]-N-methyl- (CA INDEX NAME)

810679-54-0 CAPLUS
Benzamide, 3,5-dibromo-N-[(2S)-2-(4-fluorophenyl)-4-(3-(4-hydroxy-1-piperidinyl)-1-azetidinyl)butyl}-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

RN 810679-64-2 CAPLUS
CN Benzamide,
N-{(2S)-2-(3,4-dichlorophenyl)-4-{3-(1-oxido-4-thiomorpholinyl)1-azetidinyl}butyl}-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

RN 810679-64-2 CAPLUS
CN Benzamide,
N-[(2\$)-2-(3,4-dichlorophenyl)-4-[3-(1-oxido-4-thiomorpholinyl)1-azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-72-2 CAPLUS
Benzamide, N-[2-(4-fluorophenyl)-4-[3-(1-oxido-4-thiomorpholinyl)-1-azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

810679-72-2 CAPLUS
Benzamide, N-[2-(4-fluorophenyl)-4-[3-(1-oxido-4-thiomorpholinyl)-1-azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS ON STN azetidinyl]butyl]-N-methyl- (CA INDEX NAME) (Continued)

Absolute stereochemistry.

810679-97-1 CAPLUS
Benzamide, 3,5-dibromo-N-[(2S)-2-(4-fluorophenyl)-4-[3-(4-morpholinyl)-1-azetidinyl]butyl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

810680-24-1 CAPLUS
Benzamide, 3-bromo-N-[(2S)-2-(4-fluorophenyl)-4-[3-(4-morpholinyl)-1-azetidinyl]butyl]-5-iodo-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-76-6 CAPLUS
Benzamide, N-{2-{4-fluorophenyl}-4-{3-{4-oxo-1-piperidinyl}-1-azetidinyl}butyl}-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

810679-76-6 CAPLUS
Benzamide, N-[2-(4-fluorophenyl)-4-[3-(4-oxo-1-piperidinyl)-1-azetidinyl]butyl]-N-methyl-3,5-bie(trifluoromethyl)- (CA INDEX NAME)

810679-97-1 CAPLUS
Benzamide, 3,5-dibromo-N-{(2S)-2-(4-fluorophenyl)-4-(3-(4-morpholinyl)-1-

ANSWER 9 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

B10680-24-1 CAPLUS
Benzamide, 3-bromo-N-[(2S)-2-(4-fluorophenyl)-4-(3-(4-morpholinyl)-1-azetidinyl]butyl]-5-iodo-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

REFERENCE COUNT:

THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

PORMAT

NO 2006000206 PRIORITY APPLN. INFO.:

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:1124562 CAPLUS

DOCUMENT NUMBER: 142:56156

ITILE: Preparation of heterocyclic-substituted azetidines as NKI/NKZ receptor antagonists

Johansson, Anders; Persson, Joachim

Astrazeneca Ab, Swed.

SOURCE: PCT Int. Appl., 107 pp.

CODEN: PIXXDZ

LANGUAGE: PATENT INFORMATION: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION: 1 DOCUMENT TYPE: LANGUAGE: FAMILY ACC. NUM. COUNT: PATENT INFORMATION: A2 20041223
A3 20050217
AM, AT, AU, AZ,
CU, CZ, DE, DK,
NR, HU, ID, IL,
IT, LU, LV, MA,
PG, PH, PL, PT,
RT, TT, IZ, UA,
KE, LS, MM, MZ,
KZ, MD, RU, TJ,
BP, BJ, CF, CG, PATENT NO. PATENT NO.

WO 2004110344

W: AE, AG,
CN, CC,
GE, GN,
LK, LR,
NO, NZ,
TJ, TM,
RW: BW, GR,
AZ, BY,
EE, ES,
SI, SK,
SN, TD,
AU 2004246983

CA 2529126

EP 1636221

R: AT, BE, WO 2004-SE901 BG, BR, BW, EC, EE, EG, JP, KE, KG, MK, MN, MW, SC, SD, SE, UZ, VC, VN, SL, SZ, TZ, BE, BG, CH, LU, MC, NL, GA, GN, GQ, BY, BZ, CA, CH, ES, PI, GB, GD, KP, KR, KZ, LC, MX, MZ, NA, NI, SG, SK, SL, SY, YU, ZA, ZM, ZW, UG, ZM, ZW, AM, CY, CZ, DE, DK, PL, PT, RO, SE, GW, ML, MR, NE, BA, BB, DM, DZ, IN, IS, MD, MG, RO, RU, UG, US, NA, SD, TM, AT, IE, IT, CI, CM, SN. TD. TG
4246983 A1 20041223 AU 2004-246983 20040609
9126 A1 20041223 CA 2004-2529126 20040609
6221 A2 20060322 EP 2004-736475 20040609
AT. BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PL, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, CN 1805957 BR 2004011285 JP 2006527267 MX 2005PA13276 US 2006172988 CN 2004-80016343 BR 2004-11285 JP 2006-517025 MX 2005-PA13276 US 2005-560319 NO 2006-206 20060719 20060801 20061130 20060309 20040609

SE 2003-3493 A 20031219 WO 2004-SE901 20040609 OTHER SOURCE(S):

CASREACT 142:56156; MARPAT 142:56156

SE 2003-1744

20060313

ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

810678-99-0 CAPLUS
Benzamide, 3,5-dichloro-N-{(2S)-2-(3,4-dichlorophenyl}-4-{3-(4-thiomorpholinyl)-1-azetidinyl]butyl]-N-methyl-, monoacetate (9CI) {CAINDEX NAME}

CRN 810678-98-9 CMF C25 H29 C14 N3 O S

Absolute stereochemistry

64-19-7 C2 H4 O2

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS ON STN

Title compds. 1 (Het = (un)substituted 4-7-membered heterocycle; R1 = H, OH, alkyl, etc.; R2-1 = H, alkyl, cycloalkyl, alkenyl, alkynyl, etc.; R4

alkyl, cycloalkyl, alkenyl, alkynyl; Ar = pyridinyl, naphthyl, etc.} are prepared For instance, 3,5-Dichloro-N-[(2S)-2-(3,4-dichlorophenyl)-4-(3-(thiomorpholin-4-yl)azetidin-1-yl)butyl]-N-methylbenzamide is prepared

(thiomorpholin-4-yl)azetidin-1-yl)butyl]-N-methylbenzamide is prepared steps from 1-(diphenylmethyl)azetidine-3-yl methanesulfonate, thiomorpholine, cert-Bu [(2S)-2-(3,4-dichlorophenyl)-4-oxobutyl)methylcarbamate and 3,5-dichlorobenzoic acid. Example compds. exhibit pKB 7-9 for the NKI and NK2 receptor and < 7.5 for the NK3 receptor. I are useful for the treatment of pain, depression, etc. 810678-98-9P 810679-90-10-7P 810679-01-7P 810679-02-8P 810679-03-9P 810679-04-0P 810679-05-8P 810679-03-9P 810679-04-P 810679-05-9P 810679-03-P 810679-03-P 810679-03-P 810679-05-P 810679-03-9P 810679-05-P 810679-05-P 810679-05-P 810679-05-9P 810679-05-P 810679-05-9P 810679-05-9P 810679-13-P 810679-13-P 810679-13-P 810679-13-P 810679-73-19

(preparation of heterocyclic-substituted azetidines as NK1/NK2 receptor

20051207 20051209

20030613

ptor antagonists) 810678-98-9 CAPLUS Benzamide, 3,5-dichloro-N-{(2S)-2-(3,4-dichlorophenyl)-4-{3-(4-thiomorpholinyl)-1-azetidinyl}butyl}-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-01-7 CAPLUS Benzamide, 3,5-dibromo-N-{(2S)-2-(4-fluorophenyl)-4-{3-(4-morpholinyl)-1-azetidinyl}butyl)-N-methyl-, dihydrochloride (9Cl) (CA INDEX NAME)

Absolute stereochemistry.

2 HC1

810679-02-8 CAPLUS
Benzamide, N. - (2s)-2-(3,4-dichlorophenyl)-4-(3-(4-thiomorpholinyl)-1-azetidinyl|butyl]-3,5-difluoro-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

810679-03-9 CAPLUS

Habte

ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued) Benzamide, N-[(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-thiomorpholinyl)-1-ezetidinyl]butyl]-3,5-difluoro-N-methyl-, monoacetate (9CI) (CA INDEX NAME)

CRN 810679-02-8 CMF C25 H29 C12 F2 N3 O S

Absolute stereochemistry.

810679-04-0 CAPLUS

Benzamide, N-{(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-thiomorpholinyl)-1aretidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

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RN 810679-08-4 CAPLUS
CN Benzamide,
3-cyano-N-[(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-thiomorpholinyl)-1-azetidinyl]butyl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

RN 810679-09-5 CAPLUS
CN Benzamide,
3-cyano-N-[(2S)-2-(3,4-dichlorophenyl)-4-(3-(4-thiomorpholinyl)1-azetidinyl]butyl]-N-methyl-, monoacetate (9C1) (CA INDEX NAME)

CRN 810679-08-4 CMF C26 H30 C12 N4 O S

Absolute stereochemistry.

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-05-1 CAPLUS Benzamide, N- $\{(2\$)-2-(3,4-\text{dichlorophenyl})-4-\{3-(4-\text{thiomorpholinyl})-1-\text{azetidinyl}\}$ butyl $\}-N-\text{methyl}-3,5-\text{bis}\{\text{trifluoromethyl}\}-$ , monoacetate (9CI) (CA INDEX NAME)

CM 1

CRN 810679-04-0 CMF C27 H29 Cl2 F6 N3 O S

Absolute stereochemistry.

CM 2

CRN 64-19-7 CMF C2 H4 O2

ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-16-4 CAPLUS
Benzamide, N-[2-(4-fluorophenyl)-4-[3-(4-thiomorpholinyl)-1azetidinyl]butyl]-N-methyl-3,5-bis{trifluoromethyl}- (CA INDEX NAME)

810679-17-5 CAPLUS
Benzamide, N-(2-(4-fluorophenyl)-4-(3-(4-thiomorpholinyl)-1-azetidinyl)butyl}-N-methyl-3,5-bis(trifluoromethyl)-, diacetate (9CI)

CRN 810679-16-4

ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN CMF C27 H30 F7 N3 O S (Continued)

810679-21-1 CAPLUS
Benzamide, 3-fluoro-N-[(2S)-2-(4-fluorophenyl)-4-(3-(4-morpholinyl)-1-azetidinyl)butyl)-N-methyl-5-(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

RN 810679-25-5 CAPLUS
CN Benzamide,
N-[(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-fluoro-1-piperidinyl)-1-

ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN CRN 810679-26-6 CMF C28 H31 Cl2 F6 N3 O2 (Continued)

Absolute stereochemistry

CRN 64-19-7 CMP C2 H4 O2

810679-30-2 CAPLUS
Benzamide, N-{(2S)-2-(4-fluorophenyl)-4-{3-(4-fluoro-1-piperidinyl)-1-azetidinyl}butyl}-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

Habte

ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued) azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

RN 810679-26-6 CAPLUS
CN Benzamide,
N-{(2S)-2-(3,4-dichlorophenyl)-4-(3-(4-hydroxy-1-piperidinyl)-1azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

RN 810679-27-7 CAPLUS
CN Benzamide,
N-[(2S)-2-(3,4-dichlorophenyl)-4-[3-(4-hydroxy-1-piperidinyl)-1azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)-, diacetate (salt)
(9CI) (CA INDEX NAME)

ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued) 810679-32-4 CAPLUS Benzamide, N-{(25)-3-(4-fluorophenyl)-4-(3-(4-hydroxy-1-piperidinyl)-1-azetidinyl}butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

RN 810679-33-5 CAPLUS
CN Benzamide,
3.5-dichloron-\{\( \)(2\)\}-2-\( \)(4-fluorophenyl\)\)-4-\( \)(3-\( \)(4-morpholinyl\)\)-1azetidinyl\)butyl\]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

810679-54-0 CAPLUS
Benzamide, 3,5-dibromo-N-{(2S)-2-(4-fluorophenyl)-4-{3-(4-hydroxy-1-piperidinyl)-1-azetidinyl}butyl}-N-methyl- (CA INDEX NAME)

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-55-1 CAPLUS
Benzamide, 3-bromo-N-[(2S)-2-(4-fluorophenyl)-4-(3-(4-morpholinyl)-1-azetidinyl]butyl]-5-iodo-N-methyl-, dihydrochloride (9CI) (CA INDEX

810679-62-0 CAPLUS
Benzamide, 3,5-dichloro-N-[(2S)-2-(3,4-dichlorophenyl)-4-(3-(1-oxido-4-thiomorpholinyl)-1-azetidinyl]butyl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

RN 810679-64-2 CAPLUS
CN Benzamide,
N-[(2S)-2-(3,4-dichlorophenyl)-4-[3-(1-oxido-4-thiomorpholinyl)1-azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

Absolute stereochemistry.

RN 810679-65-3 CAPLUS
CN Benzamide,
N-{(25)-2-{3,4-dichlorophenyl}-4-{3-(1-oxido-4-thiomorpholinyl}1-azetdinyl}butyl}-N-methyl-3,5-bis(trifluoromethyl)-, monoacetate (9CI)
(CA INDEX NAME)

CM 1

CRN 810679-64-2 CMF C27 H29 C12 F6 N3 O2 S

Absolute stereochemistry.

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810679-63-1 CAPLUS
Benzamide, J, 5-dichloro-N-[(2S)-2-(3,4-dichlorophenyl)-4-[3-(1-oxido-4-thiomorpholinyl)-1-azetidinyl]butyl]-N-methyl-, monoacetate (9CI) (CAINDEX NAME)

CRN 810679-62-0 CMF C25 H29 C14 N3 O2 S

Absolute stereochemistry

СМ

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN

CRN 64-19-7 CMF C2 H4 O2

810679-72-2 CAPLUS
Benzamide, N-[2-(4-fluorophenyl)-4-[3-(1-oxido-4-thiomorpholinyl)-1-azetidinyl]butyl]-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

810679-73-3 CAPLUS

Benzamide, N-[2-(4-fluorophenyl)-4-[3-(1-oxido-4-thiomorpholinyl)-1azetidinyl]butyl]-N-methyl-3,5-bie(trifluoromethyl)-, monoacetate (9C1)
(CA INDEX NAME)

CH 1

CRN 810679-72-2 CMF C27 H30 F7 N3 O2 S

ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

– с– сн³ 0 HO-

810679-76-6 CAPLUS
Benzamide, N. (3-(4-fluorophenyl)-4-(3-(4-oxo-1-piperidinyl)-1azetidinyl)butyll-N-methyl-3,5-bis(trifluoromethyl)- (CA INDEX NAME)

810679-97-1 CAPLUS
Benzamide, 3,5-dibromo-N-[{2S}]-2-{4-fluorophenyl}-4-{3-(4-morpholinyl}-1-azetidinyl}butyl]-N-methyl- (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN ACCESSION NUMBER: 2003:442765 CAPLUS DOCUMENT NUMBER: 139:245960 1TITLE: 4-Amino-2-(aryl)-butylbenzamid

2003:442765 CAPLUS
139:245960
4-Amino-2-(aryl)-butylbenzamides and Their
conformationally constrained analogues. Potent
antagonists of the human neurokinin-2 (NK2) receptor
MacKenzie, A. Roderick; Marchington, Allan P.;
Middleton, Donald S.; Newman, Sandre D.; Selway,
Christopher N.; Terrett, Nicholas K.
Department of Discovery Chemistry, Pfizer Global
Research and Development, Sandwich, Kent, CT13 SNJ, AUTHOR (S):

CORPORATE SOURCE:

UK SOURCE:

Bioorganic & Medicinal Chemistry Letters (2003), 13(13), 2211-2215 CODEN: BMCLE8; ISSN: 0960-894X Elsevier Science B.V. Journal English CASREACT 139:245960

PUBLISHER: DOCUMENT TYPE: LANGUAGE:

OTHER SOURCE(S):

III

A library, evaluating a range of piperszines, piperidines and acyclic amines, as replacements for the 4-hydroxy-4-phenylpiperidine moiety in lead I. (RI = Ph, R2 = OH) was prepared These efforts identified the 4-(1-benzimidazolone)piperidine analog I (RI = 1-benzimidazolonyl, R2 =

which was further optimized using classical single-compound synthesis to yield the 3-(4-morpholino)azetidine II. Conformationally constrained

ANSWER 10 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

810680-24-1 CAPLUS
Benzamide, 3-bromo-N-{(2S)-2-(4-fluorophenyl)-4-{3-(4-morpholinyl)-1-azetidinyl}butyl}-5-iodo-N-methyl- (CA INDEX NAME)

ANSWER 11 OF 11 CAPLUS COPYRIGHT 2007 ACS on STN (Continued) analogs of II, III (R = PhCO, n = 0; R = PhCO, 4-MeOC6H4, PhSO2, etc., n L4

1), generally offered no potency advantage in this particular series. 596105-92-9P ΙT

REFERENCE COUNT:

FORMAT

THERE ARE 22 CITED REFERENCES AVAILABLE FOR

RECORD. ALL CITATIONS AVAILABLE IN THE RE